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EXAMINER	
HOWARD, ZACHARY C	

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1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,892	GOLZ ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,25 and 27-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11,25 and 27-30* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☒ Claim(s) *1-4,6-11,25 and 27-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 12/27/07 has been entered in full. Claims 1, 2, 3 and 25 are amended. Claim 5, 12-24 and 26 are canceled. New claims 27-30 are added.

Claims 1-4, 6-11, 25 and 27-30 are under consideration in the instant application.

Information Disclosure Statement

The Information Disclosure Statement of 12/27/07 has been considered.

Withdrawn Objections and/or Rejections

All rejections of claim 5 are moot in view of Applicants' cancellation of this claim.

The objections to claims 1-3 at pg 2 of the 9/27/07 Office Action are *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 25 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was set forth at pg 3-12 of the 9/27/07 Office Action for claims 1-4, 6-11 and 25; new claims 27-30 are herewith added.

Applicants' arguments (12/27/07) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that it was known in the prior art that "modulation of intracellular Ca^{2+} controls cardiac myocyte contraction" and that the "skilled artisan would have understood the correlation between modulating intracellular Ca^{2+} and controlling critical aspects of cardiovascular function, such as cardiac contraction" (pg 10). Applicants quote the first two lines from Bers (2000) in support of this argument. Applicants further argue that the prior art (Bonini et al) teaches that "NPFF1 modulates intracellular Ca^{2+}" and that the instant specification teaches that "NPFF1 is highly expressed in various cardiac tissues", including aorta, left ventricle, right and left atria, and pericardium. Applicants argue that "thus, no undue experimentation would be needed for the skilled artisan to associate the NPFF1 receptor with cardiovascular diseases" (pg 11).

Applicants' arguments have been fully considered but are not found persuasive. The system of "Cellular Ca Fluxes" involved in "activation of myofilament force", as depicted by Bers in Figure 1a, includes changes intracellular calcium concentrations but does not include NPFF1 or any other GPCR. Furthermore, Bers teaches, "these systems are also subject to many regulatory influences (not discussed here). The result is a rich variation in functional behavior that allows the heart to function effectively, but this also continues to pose many challenges to understanding this complex system under diverse conditions. Important remaining questions include the molecular mechanism of ECC, how the release channel is regulated physiologically, how alterations in Ca^{2+} handling in disease states lead to mechanical dysfunction and arrythmias, and what are the best molecular targets for therapeutics" (pg 279). Thus, Bers teaches that the role of intracellular calcium in cardiovascular disease is poorly understood. Therefore, the skilled artisan at the time of filing of instant application would not have sufficient understanding to use modulation of calcium as a treatment for heart disease. Furthermore, Applicants show expression of NPFF1 in some heart tissues, yet this information is not sufficient for the skilled artisan at the time of filing to use a modulator of NPFF1 to treat a cardiovascular disease. Bonini shows intracellular calcium activation using an artificial system wherein NPFF1 was transfected into COS-7 cells and contacted with a ligand *in vitro*. This does not provide evidence that NPFF1

actually modulates intracellular calcium levels in heart tissue, or that such modulation (if it exists) functions in such a manner that it could be used to treat any or all cardiovascular diseases.

It is maintained that based on the limited teachings of the specification and prior art, the skilled artisan would not be able to predict whether or not a modulator of an NPFF1-activity (such as alteration of intracellular calcium) could be used to treat a cardiovascular disease. Neither the specification nor the prior art teach provide any reasonable correlation between NPFF1 activity and cardiovascular diseases (either in a general or any species disease). The skilled artisan would recognize that gene expression in a particular tissue does not necessarily indicate that the encoded protein has a role in a disease associated with said tissue. A gene can be expressed in a tissue without having a role in a particular disease associated with that tissue. As shown by Applicants' working examples, NPFF1 is expressed in a wide variety of tissues, with the highest levels of expression in many tissues other than heart tissues. It is possible that NPFF1 activity has a role in said tissues that is entirely unrelated to any disease associated with said tissues. As set forth previously, Juhasz et al (2002; cited previously) demonstrate that thousands of different genes are expressed in tissues of the cardiovascular system (pg 689). The skilled artisan could not predict which, if any, of these expressed genes is associated with one or more cardiovascular diseases. Even if a particular gene is found to have a role in healthy tissue (e.g., healthy heart tissue), the skilled artisan could not predict whether or not it would also have a role in a cardiovascular disease, such that modulating its activity would treat said disease. As such, it is not predictable whether or not a modulator of NPFF1 could be used to treat one or more cardiovascular diseases. Furthermore, the specification provides no guidance as to whether an agonist or an antagonist of NPFF1 would provide the therapeutic treatment for a cardiovascular disease. In order to use the claimed method to identify a therapeutic, the skilled artisan would need to first practice the claimed method to identify a modulator of the calcium mobilization of NPFF1, and then engage in further undue experimentation to test whether or not the modulator could be used to treat one or more cardiovascular diseases.

Applicants further argue (pg 9) that claim 1 is "simply a screening method for compounds which bind to a human NPFF1 polypeptide" and "does not require identification of a test compound which binds to a human NPFF1 polypeptide as also able to alter NPFF1 activity".

Applicants' arguments have been fully considered but are not found persuasive. The claimed method is not "simply a screening method"; instead it is a screening method that recites the intended use of identifying compounds that may be useful in treating a cardiovascular disease. If an intended use is recited, it must meet the meet the requirements of 35 U.S.C. 112, first paragraph. Identification of a test compound that can bind to an NPFF1 polypeptide does not allow the skilled artisan to predict whether or not said binding partner can also alter an activity of the NPFF1 polypeptide. A test compound can bind to a receptor without altering its activity. The skilled artisan would still need to test said binding partner in an assay that measured the ability of the binding partner to modulate NPFF1 activity. The specification does not teach a use for binding agents that do not also modulate NPFF1 activity.

Applicants further argue that working examples are not required to enable an invention and point to *In re Long* (1966) in support, and argue that "lack of a working example should not be given undue weight because the inventors have provided adequate direction for carrying out the claimed methods". Applicants further argue that the previous Office Action did not provide a reasonable basis to question the enablement of the claims.

Applicants' arguments have been fully considered but are not found persuasive. The lack of a working example was not given undue weight in the rejection set forth previously and maintained herein; instead, the presence or absence of working examples was merely one consideration included in the *Wands*-type analysis set forth in the rejection. It is maintained herein that said analysis provided a reasonable basis to question the enablement of the claims.

Furthermore, Applicants' response contains no arguments with respect to the following portion of the rejection set forth previously. Even if the claimed methods were enabled for a method of screening to identify a therapeutic using a polypeptide of SEQ

ID NO: 2 (or residues 103-522 of SEQ ID NO: 2 as taught by Bonini), they would lack enablement for a method of screening using other variants of SEQ ID NO: 2 for the reasons set forth previously. Each of the amended claims encompasses use of a vast genus of variant “human NPFF1” polypeptides. As set forth previously, the specification teaches that an “NPFF1 polypeptide” includes not only a polypeptide of SEQ ID NO: 2 but also variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide “has NPFF1 activity” (pg 9, lines 1-15). The polypeptide of SEQ ID NO: 2 consists of 522 amino acids; therefore, a variant with 80% homology has 104 amino acids that differ from SEQ ID NO: 2. The amendment to limit the claims to "human NPFF1" does not change the scope of the claims with respect to SEQ ID NO: 2, because SEQ ID NO: 2 is a human NPFF1 sequence. Prior art was cited teaching that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (Wells (1990); Ngo et al (1995); each cited previously). Prior art was also cited teaching that the art recognizes that function cannot be predicted from structure alone (Bork (2000); Skolnick et al (2000); Doerks (1998); Smith and Zhang (1997); Brenner (1999); Bork et al (1996); each cited previously). In view of the limited teachings of specification regarding the nature of active variants of SEQ ID NO: 2 and the teachings of the relevant art regarding the difficulty in predicting functional variants of a protein it would require undue experimentation to make and test (for "NPFF1 activity") each member of the vast genus of variants encompassed by the claims.

With respect to claims 1-4 and 6-11, it is noted that the portion of the enablement rejection directed to non-isolated host cells is moot in view of Applicant's amendments to independent claims 1, 2 and 3 that limit the contacting step of the methods to "in vitro". However, independent claim 25 still encompasses identifying a regulator of NPFF1 using *in vivo* methods of screening. The specification clearly contemplates transgenic animals with cells exogenously expressing the polypeptides of the invention (Example 14, pg 99-100). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with an NPFF1 gene is demonstrated to express the encoded peptide. The unpredictability of the art is very

high with regards to making transgenic animals (Wang et al, 1999; Kaufman et al, 1999; each cited previously). It is maintained for the reasons set forth previously that due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed protein, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-4, 6-11, 25 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 12-15 of the 9/27/07 Office Action for claims 1-4, 6-11 and 25; new claims 27-30 are herewith added to the rejection.

Applicants' arguments (12/27/07) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that independent claims 1-3 and 25 have been amended to limit NPFF1 polypeptides to human NPFF1 polypeptides, which Applicants argue was well known in the art before the priority date of the application. Applicants point to *Capon v. Eshhar* (2005) in support of the argument that "written description of a gene which is well known in the art does not require a structural recitation either in the specification or in the claims" and "a sequence identifier for a well-known protein such as NPFF1 should also not be required". Applicants argue that the skilled artisan would "readily recognize the genus of human NPFF1 polypeptides because these polypeptides were known in the art". Applicants further argue that the rejection does not

set forth express findings of fact to provide reasons why a skilled artisan would not have recognized that the inventor was in possession of the invention at the time of filing, as required by MPEP § 2163.04.

Applicants' arguments have been fully considered but are not found persuasive. The rejection set forth in previous Office Action did set forth fact-based reasons why a skilled artisan would not have recognized that the inventor was in possession of the invention at the time of filing, as required by MPEP § 2163.04. The rejection set forth in previous Office Action did not require a sequence identifier for the NPFF1 polypeptide used in the claim methods, which as acknowledged was known in the prior art. Instead, the rejection set forth reasons why each of the claims is a genus claim that encompasses use of a genus of variant "NPFF1" polypeptides. As set forth previously, the specification teaches that an "NPFF1 polypeptide" includes not only a polypeptide of SEQ ID NO: 2 but also variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF1 activity" (pg 9, lines 1-15). The polypeptide of SEQ ID NO: 2 consists of 430 amino acids; therefore, a variant with 80% homology has 86 amino acids that differ from SEQ ID NO: 2. The amendment to limit the claims to "human NPFF1" does not change the scope of the claims with respect to SEQ ID NO: 2, because SEQ ID NO: 2 is a human NPFF1 sequence. The instant specification fails to describe the entire genus of variant human NPFF1 polypeptides that will function in the claimed methods (i.e., which mutations of the prior art sequence will retain an "NPFF1 activity"). Therefore it is maintained for the reasons set forth in the 9/4/07 Office Action that only methods of screening comprising use of a polypeptide of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-11, 28 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonini et al, 2000. Journal of Biological Chemistry. 275(50): 39324-39331; cited previously. This rejection was set forth at pg 15-18 of the 9/27/07 Office Action for claims 1-4 and 6-11; new claims 28 and 30 are herewith added.

The rejection is first restated in view of Applicants' amendments to the claims and then Applicants' arguments are addressed.

Applicants have amended the preamble of claim 1 to "A method of screening for agents that may be useful in the treatment of a disease selected from … in a human". The elected species of disease under consideration is “cardiovascular diseases”. It is maintained that the preamble is an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. See MPEP 2111.02, “Effect of Preamble”, section II, “Preamble Statements Reciting Purpose or Intended Use”. As such, the method of claim 1 encompasses a method comprising the recited method steps.

As described previously, Bonini et al (2000) teach a human NPFF1 polypeptide (see Figure 1) that is 100% identical to residues 1-430 of instant SEQ ID NO: 2 (an alignment of the two sequences was attached to 9/27/07 Office Action as Sequence Alignment #1). Bonini et al further teach, “Membranes from transiently transfected COS-7 cells exhibited high affinity, saturable [I^{125}]1DMeNPFF binding for both NPFF1 and NPFF2” (pg 39327). As such, Bonini et al teach a method of contacting a test compound ([I^{125}]1DMeNPFF) with a NPFF1 polypeptide and detecting binding of said test compound to said NPFF1 polypeptide. The teachings of Bonini meet all of the limitations of the method steps of amended claim 1 for the following reasons.

Step (i) of claim 1 has been amended to limit the contacting performed to *in vitro* and with a human NPFF1 polypeptide. The binding assay taught by Bonini was performed *in vitro* using membranes from transfected COS-7 cells (see above). Therefore, the teachings of Bonini meet the limitations of step (i) of amended claim 1.

Step (ii) of claim 1 has not been amended. As set forth previously, the term "detecting binding" in step (ii) is broadly interpreted to encompass a "detection" step (i.e., detecting whether or not binding has occurred).

New step (iii) has been added that recites "identifying a test compound that binds to said NPFF1 as agent that may be useful in the treatment of the disease." However, the teachings of Bonini meet this limitation for the following reasons. Step (iii) is a mental identification that only applies to a binding compound and does not result in a physical manipulation of the binding compound; thus the new step does not render the claimed method as patentability distinct from the method taught by Bonini. Furthermore, the new step only requires that the agent may be useful to treat cardiovascular disease; the converse of "may" is "may not"; thus, this recitation inherently applies to all binding compounds because they all "may" or "may not" be useful in the recited manner. The method of Bonini teaches screening for test compounds that bind; any compound so identified inherently may (or may not) be useful in the recited treatment.

The method of amended claim 2 encompasses a method of screening comprising determining the activity of a human NPFF1 polypeptide a certain concentration of a test compound or in the absence of said test compound, and determining the activity of said polypeptide at a different concentration of said test compound, and identifying the test compound as a potential therapeutic agent useful in the treatment of the disease if the activity of the NPFF1 polypeptide is different, and wherein the activity of the polypeptide results in an alteration of intracellular calcium. Bonini et al further teach, "functional studies monitoring intracellular Ca^{2+} fluxes with hNPFF1 [human NPFF1] and hNPFF2 were conducted, using a fluorescence imaging plate reader, with transiently transfected COS-7 cells co-expressing either NPFF1 or NPFF2 and $G\alpha_{q/z5}$. NPFF elicited an increase in intracellular Ca^{2+} when either hNPFF1 or hNPFF2 were transfected … PQRF amide acted as a full agonist in cells expressing

either the NPFF1 or NPFF2 receptors" (pg 39328). The activity in the presence of PQRF amide is compared to the absence of PQRF amide (i.e., in the presence of NPFF but not PQRF amide) in Table II. Step (iii) of claim 2 recites that any test compound that can alter activity is identified as a "potential therapeutic". However, the teachings of Bonini meet this limitation for the following reasons. Step (iii) is a mental identification that only applies to an activity-altering compound and does not result in a physical manipulation of the binding compound; thus the new step does not render the claimed method as patentability distinct from the method taught by Bonini. Furthermore, the new step only requires that the agent is a potential therapeutic useful in treatment of disease; thus, this recitation inherently applies to all activity-altering compounds because they all are potentially useful in the recited manner. The method of Bonini teaches screening for test compounds that alter activity; any compound so identified inherently potentially could be used in the recited treatment. As such, Bonini et al teach a method that anticipates instant claim 2.

The method of amended claim 3 encompasses a method of screening comprising determining the activity of a human NPFF1 polypeptide at a certain concentration of a test compound, determining the activity of said NPFF1 polypeptide in the presence of a compound known to be a regulator of a NPFF1 polypeptide, and identifying the test compound as a potential therapeutic agent useful in treatment if the activity of the NPFF1 polypeptide is different, and wherein the activity of the polypeptide results in an alteration of intracellular calcium. Table II of Bonini et al demonstrates the activity of a compound (PQRF-amide) in comparison to NPFF in activation of intracellular calcium mobilization. This compound acts as an agonist of the NPFF1 receptor with a higher EC_{50} and lower response than NPFF. Therefore, Bonini teaches a method comprising determining the activity of NPFF1 polypeptide at a certain concentration of a test compound (PQRF-amide) and determining the activity of said NPFF1 polypeptide in the presence of a compound known to be regulator of a NPFF1 polypeptide (NPFF, known to be a regulator of NPFF1 in view of the results described above). As with claim 2, new method step (iii) is an inherent feature of the teachings of Bonini. As such, Bonini et al teach a method that anticipates instant claim 3.

Claim 4 depends from claim 1 and limits the contacting step to "at the surface of a cell". Bonini further teaches binding assays using the hNPFF1 receptor expressed in HEK-293 cells (pg 38327). The NPFF1 receptor is a cell membrane expressed GPCR; therefore, the contacting step occurs at the cell surface. As such, the teachings of Bonini et al also anticipate claim 4.

Claim 6 depends from claim 1 and limits the method to one wherein "the step of contacting is in a cell-free system". As described above, Bonini et al teach binding assays using membranes from COS-7 cells. Isolated cell membranes meet the definition of a "cell-free system". As such, the teachings of Bonini et al described above also anticipate claim 6.

Claim 7 depends from claim 1 and limits the method to one wherein "the polypeptide is coupled to a detectable label". The phrase "coupled" broadly encompasses any form of binding, and the phrase "detectable label" encompasses a radiolabeled ligand. As such, the binding assays described by Bonini et al, wherein a radiolabeled ligand binds to the NPFF1 receptor, meet the definition of a coupling to a detectable label. As such, the teachings of Bonini et al described above also anticipate claim 7.

Claim 8 depends from claim 1 and limits the compound to a compound coupled to a detectable label. As described above, the NPFF test compound used by Bonini et al is coupled to a detectable [I^{125}] label. As such, the teachings of Bonini et al described above also anticipate claim 8.

Claim 9 depends from claim 1 and limits the method to one wherein, "the test compound displaces a ligand which is first bound to the polypeptide". Bonini further teaches, competition binding assays wherein several ligands are test for the ability to displace the ligand [I^{125}]1DMeNPFF (see Table I on pg 39328). As such, the teachings of Bonini et al described above also anticipate claim 9.

Claims 10 and 11 each depend from claim 1 and respectively limit the method to one wherein, "the polypeptide is attached to a solid support" (claim 10) or "the compound is attached to solid support" (claim 11). The claims do not limit the step at which the polypeptide is attached to a solid support; therefore, the claim broadly

encompasses a method wherein the polypeptide or compound is attached to a solid support after incubation with the ligand. Furthermore, the claims encompass direct or indirect (e.g., via another compound) attachment. The membrane binding assays conducted by Bonini et al result in both the membrane-bound receptor and ligand being deposited on a "double layer of glass fiber filters", which are used for scintillation counting to measure the quantity of radiolabeled ligand that bound to the receptor. Glass fiber filters meet the definition of a solid support. Therefore, Bonini et al teach a binding assay which results in the NPFF1 polypeptide and the radiolabeled NPFF ligand each being attached to a solid support. As such, the teachings of Bonini et al described above also anticipate each of claims 10 and 11.

New claims 28 and 30 depend from claims 2 or 3 (respectively) and each limit the method of the parent claim to one wherein the polypeptide (NPFF1) is coupled to a detectable label. In the teachings of Bonini described above with respect to claims 2 or 3, the NPFF1 polypeptide is coupled to a ligand (NPFF, FPP or PQRF-amide), each of which is a detectable label.

In the response, Applicants argue (at pg 11-12) that Bonini does not meet the standards set forth in *Verdegaal Bros v. Union Oil of California* (1987) or *Richardson v. Suzuki Motor Co* (1989). Applicants point to the amendments to claim 1 and argue that Bonini does not teach any association with human NPFF1 with cardiovascular disease.

Applicants' arguments have been fully considered but are not found persuasive. The Examiner does not dispute the standards set forth in *Verdegaal* or *Richardson*. The rejection meets these standards, even in view of the amended claims, for the reasons set forth above. Bonini teaches, in as complete detail, each and every element of an identical invention as set forth in the claims. Furthermore, for the reasons set forth above, Bonini does not need to specifically teach an association with human NPFF1 and cardiovascular disease; the recitations in the claims that refer to such an association are either intended uses or inherent features of binding compounds.

New rejections necessitated by Applicants' amendment

Claim Objections

Claim 3 is objected to because of the following informalities:

In claim 3, line 11, the recitation of "is similar to than the activity of the NPFF1 polypeptide" contains the extraneous word "than".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, *1st paragraph, new matter*

Claims 27 and 29 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

New claims 27 and 29 depend from claims 2 or 3 (respectively) and each recite "wherein the step of contacting is in a cell-free system". However, each parent claim (2 or 3) has been amended to by limited to a method of screening by determining the activity of an NPFF1 polypeptide, "wherein the activity of the polypeptide results in an alteration of intracellular calcium or alteration of inositol phosphate concentration". Thus, dependent claims 27 and 29 are limited to methods of screening wherein intracellular calcium (i.e., calcium inside a cell) is measured in a cell-free system (i.e., a system without cells and therefore without an "intracellular" locale). At pg 1 of the 12/27/07 response, Applicants indicate that support for new claims 27-30 can be found in claims 4 and 6 as originally filed. However, while original claim 6 was directed to assay in a cell-free system, and depended from claims 2 and 3, original claims 2 and 3 did not comprise an activity that is alteration of intracellular calcium. The entire specification has been reviewed and no support for new claims 27 or 29 has been found. The specification discusses assays wherein intracellular activity is measured; however, these assays are all described as being cell-based rather that cell-free (see ¶ [0171] of the published application). The specification discusses cell-free assays; however, none of these assays is described as involving alteration of intracellular calcium (see ¶ [0172] of the published application). Nowhere does the specification describe an assay with the specific combination of cell-free assay and an activity of alteration of intracellular

calcium, nor does the concept of the specific assay flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for the method encompassed by new claims 27 and 29.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646